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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/817,507	04/17/97	KISHIMOTO T	53466/201

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EXAMINER	
REEVES, J	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/817,507	Applicant(s) Kishimoto et al
	Examiner Julie E. Reeves, Ph.D.	Group Art Unit 1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-14* _____ is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14* _____ is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☑ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. As of February 7, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1642, Technology Center 1600.

2. Claim 10 has been amended. Claims 1-14 are pending and under examination.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention (i.e., a composition and not a method) to which the claims are directed.

4. The disclosure is objected to because of the following informalities: The first line of the specification needs to be amended to show that this application is a 35 U.S.C. 371 national stage filing of international application PCT/JP95/02169 filed 10/20/95.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

5. Claims 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 11 and 14 are indefinite for reciting the laboratory designation "PM-1" because other laboratories/inventors may use the same laboratory designation to refer to different

antibodies. Amendment of the claim to insert the corresponding ATCC or other deposit accession number would overcome this rejection.

b. Claims 13-14 are indefinite for reciting "a reshaped human antibody" or "reshaped human PM-1 antibody" because it is not clear whether a human antibody or a humanized antibody is intended. As evidenced by Hirata et al (J Immunology Vol 143(9):2900 11/89), the PM-1 antibody that binds human interleukin-6 receptor (IL-6R) was raised by immunizing mice (page 2900, col 2, second full paragraph) and thus is a murine antibody.

c. Claims 12 is indefinite for reciting "chimeric" as the exact meaning of the word is not known. The term chimeric is generic to a class of antibodies which are products of genetic shuffling of antibody domains and other active proteins, but also encompasses proteins which comprise parts of other molecules, such as immunotoxins, fusion proteins and radiolabeled antibodies. Thus the term encompasses antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies including but not limited to CDR grafted antibodies. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

6. The claims 11 and 14 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence

that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

a. It is unclear if a cell line which produces an antibody having the exact chemical identity of PM-1 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

b. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species PM-1. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

7. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising the antibody and physiological saline, does not reasonably provide enablement for the claimed pharmaceutical compositions for the prevention or treatment of the various diseases recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claims are broadly drawn to a pharmaceutical composition for prevention or treatment of diseases caused by interleukin-6 (IL-6) production comprising an antibody to interleukin-6 receptor (IL-6R). Enablement of a "pharmaceutical composition" is considered to rest on a teaching of in vivo administration for purposes consistent with the intended use disclosed in the specification. The claims read upon the treatment or prevention of IL-6 induced disease in humans. The disclosed intended use for the broadly claimed pharmaceutical compositions is for the treatment or prevention of diseases caused by interleukin-6 production, such as

plasmacytosis, hyperimunoglobulinemia, anemia, nephritis, cachexia, rheumatism, Castleman's induced plasmacytosis and mesangium proliferative nephritis.

c. At the time the invention was made, pharmaceutical compositions comprising the claimed anti-IL-6R were not routinely used for the prevention of diseases caused by IL-6 production. As evidenced by Durum "All the aforementioned complex in vitro interactions of cytokines make it virtually impossible to predict the in vivo activities of a given cytokine. This is amply illustrated by the unexpectantly broad spectrum of in vivo activities of cytokines such as IL-1, TNF, TGF-beta and IL-6. The actual physiological role of most of the cytokines remains to be established. In fact we have to relearn the trite but true import of *"in vivo veritas*" (Paul, Fundamental Immunology, Third Edition, Chapter 21, Proinflammatory Cytokines and Immunity, page 826, first column, first and second full paragraphs). Durum also teaches that the IL-6R contains the gp130 subunit which is found in several other cytokine receptors including those for LIF, oncostatin M, IL-11 and ciliary neutrophilic factor (page 813).

d. Additionally, Henderson cautions that because of the "enormously high affinities of binding between cytokines and their receptors", "no pharmaceutical company has yet devised a cytokine receptor antagonist" (page 521, col 2 first full paragraph). Henderson disclose that the development of clinically useful cytokine antagonists would require "a novel approach"(page 521, col 2, first full paragraph). Henderson concludes that "our expectation that blocking single cytokines (by complex agents such as cloned chimaerised antibodies or soluble receptor-antibody complexes) can inhibit tissue pathology should remain at a sensible low level. Only time will tell if

it is possible to inhibit complex cytokine induced pathology in man by removing single cytokines" (page 522, final paragraph). One skilled in the art would reasonably expect that the prevention or treatment of diseases caused by cytokine production would be unpredictable for the reasons provided by Henderson and Durum,

e. Although the specification discloses the claimed composition, and general methods for formulating compositions in physiological saline (pages 9-10, bridging paragraph), there is insufficient guidance which would enable one skilled in the art to use the claimed compositions for their intended purpose, *viz.*, for the prevention or treatment of the various diseases listed in the claims. The specification has not provided adequate support to establish that the animal model data of the specification correlates with in vivo efficacy in humans. The specification shows that administration of an IL-6R antibody to transgenic mouse which had been altered to express human IL-6 resulted in suppression of the onset of nephritis, serum indicators of cachexia, suppression of the onset of plasmacytosis and anemia (Example 1, pages 12-24). Examples 2 and 3 showed that administration of an IL-6R antibody to nude mice bearing an xenograft tumor in the form of a tumor block or squamous carcinoma cell line resulted in suppression of anemia and cachexia indicators (pages 25-26). These animal models have limited predictive value for determining efficacy of preventing or treating diseases in humans, as evidenced by Strassman and Gura below.

f. The specification lacks sufficient guidance by way of general methods or working examples which teach an effective amount of the anti-IL-6 R antibody which would be used for

the treatment or prevention of the variety of diseases caused by IL-6 production. The criticality of a working example encompassing all of the method steps, especially in the prevention or treatment of IL-6 caused diseases, is underscored by Gura et al (Science Vol 278 11/97 1041-1042) in a discussion of potential shortcomings of extrapolating from in vitro studies and animal studies to similar procedures in cancer patients. Gura et al teaches that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, second col, second full paragraph) and that there were "gross difference in sensitivity in real tumors in mice and in the clonogenic assay" (page 1042, second col, second full paragraph). Further, Gura teaches that clonogenic assays "cannot tell researchers how anticancer drugs will act in the body" (page 1042, first-second col, bridging paragraph). One skilled in the art would reasonably conclude that data obtained in IL-6 inhibition data obtained in mouse xenograft studies would not correlate with results expected in humans patients because of the teachings of Gura and in view of the complexity of cytokine interactions as evidenced by Durum and Henderson.

g. Further, the disclosure does not provide working examples wherein all of the steps required to practice the method are employed. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer. The two different animals models described in the specification and used to demonstrate the affect of administering IL-6R antibody are both insufficient to demonstrate that administration of IL-6R antibody in humans would treat or prevent diseases caused by IL-6 production. As evidenced by Strassman et al, transgenic animal studies may express distorted amounts of cytokines (pages 107-

108, bridging paragraph) and one skilled in the art would reasonably conclude that the level and stability of hIL-6 expressed in the transgenic mice may not be comparable to the level and stability of IL-6 causing diseases in humans. Gura (cited above) discusses the unpredictability of correlating results obtained in mouse xenograft models with those expected in humans. Thus one skilled in the art would reasonable expect that the data obtained from transgenic mouse model of Example 1 and the xenograft nude mice models of Examples 2-3 is not sufficient to enable the broadly claimed pharmaceutical composition.

h. In the instant case, the claims are so broadly drawn, the guidance is so limited, and the art is so unpredictable that skilled artisan is presented with a multitude of un-linked alternatives with no guidance as to which will enable use of the invention as claimed. Among these are (i) whether the transgenic mice express comparable amounts of IL-6 as humans which need the claimed prophylactic or therapeutic treatment, (ii) how to correlate the results obtained in the mouse xenograft models with those expected in human patients, (iii) how to inhibit IL-6 from binding to the IL-6R without interrupting the binding of LIF, oncostatin M or other cytokines from binding to their receptors which share the gp130 subunit with IL-6R, (iv) which of many diseases to select, and (v) what dosage, schedule, and route of administration will provide a successful prophylactic or therapeutic outcome for the myriad of diseases encompassed by the claims.

i. Given the teachings of Durum, Gura, Henderson and Strassman et al which demonstrate the unpredictability in the immunotherapeutic art for inhibition of cytokine induced

diseases, and in view of the inadequate guidance and working examples, one of ordinary skill in the art would not be able to use the broadly claimed invention for preventing or treating IL-6 caused diseases without undue experimentation. Therefore, the specification fails to provide an enabling disclosure commensurate in scope with the claimed subject matter. Amending the claims to recite a composition comprising the antibody in a physiological saline would obviate this rejection.

Claim Rejections - 35 U.S.C. § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (f) he did not himself invent the subject matter sought to be patented.

9. Claims 1-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Sato et al (Cancer Res 53:851 Feb 1993).

a. Claims 1-14 recite a pharmaceutical composition which comprise an antibody specific for the IL-6R. Other embodiments include wherein the antibody is a monoclonal antibody, a chimeric antibody, a reshaped human antibody and a reshaped human PM-1 antibody. Claim 12 is being interpreted as an antibody which comprises portions from two different

sources, such as human and rodent portions. Claim 13 recites a reshaped human antibody which is being interpreted as a reshaped humanized antibody for the purposes of the art rejections.

b. When the claim is directed to a product, the preamble or intended use is generally nonlimiting if the body of the claim is directed to an old composition and the preamble merely recites a property inherent in the old composition. [*Kropa v. Robie*, 88 USPQ 478, 480 - 81 (CCPA 1951); see also MPEP 2111.02]. Thus, art which reads on a compound may also be applied to compositions consisting essentially of IL-6R antibody.

c. Sato (1993) teach the monoclonal antibody PM-1 specific for human IL-6R and teach the reshaped, humanized PM-1. See Abstract, Materials and Methods, Figure 2. Thus, the prior art reference fully discloses to the public the subject matter of the claimed invention.

10. Claim 14 is rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

a. Claim 14 recites a pharmaceutical composition, wherein the antibody is a reshaped, human PM-1 antibody.

b. Sato et al (1993) explicitly teach humanizing and reshaping the IL-6R antibody PM-1. See Abstract, Materials and Methods, Figure 2. It is noted that none of the authors Sato, Tsuchiya, Saldanha, Koishihara, Ohsugi and Bendig listed in Sato et al (1993) are included as inventors on this application. Further, it is noted that neither of the inventors Asao Katsume and Hiroyuki Saito appear in the list of authors of reference Sato 1993, nor are they cited in the

acknowledgments. Therefore it is not clear that inventors Kishimoto, Katsume and Saito invented the reshaped humanized PM-1 antibody recited in claim 14.

11. Claims 1-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Sato et al (Molecular Immunology Vol 31(5):371-81 April 1994).

a. The claims have been described above.

b. Sato (1994) teach reshaped humanized IL-6R antibody AUK12-20.

See Abstract, Materials and Methods, Figure 4. Thus, the prior art reference fully discloses to the public the subject matter of the claimed invention.

12. Claims 1-11 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hirata et al (J Immunology Vol 143(9):2900-2906, Nov 1989).

a. The claims 1-11 read upon compositions which comprise an antibody specific for the IL-6R. Other embodiments include wherein the antibody is a monoclonal antibody and wherein the antibody is PM-1.

b. Hirata et al disclose the anti-IL-6 receptor antibody designated PM-1 and demonstrate the this antibody binds to the receptor in competition with IL-6 (see Abstract). Hirata et al discloses the "Generation and characterization of anti-human IL-6R mAb PM-1" (see bridging paragraph, page 2900-2901). Thus, the prior art references fully disclose to the public the subject matter of the claimed invention.

13. Claim 11 is rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

a. Claim 11 reads upon a composition comprising the PM-1 antibody.

b. As noted above, Hirata et al explicitly disclose production of the IL-6 receptor antibody designated PM-1. However, none of the authors Hirata, Taga, Hibi, Nakano and Hirano are included as inventors on this application. Further, it is noted that neither of the inventors Asao Katsume and Hiroyuki Saito appear in the list of authors of reference Hirata et al, nor are they cited in the acknowledgments. Therefore it is not clear that inventors Kishimoto, Katsume and Saito invented the PM-1 antibody recited in claim 11.

14. Claims 1-10 are rejected under 35 U.S.C. § 102(a) as being anticipated by Tamura et al (Proc Natl Acad Sci USA Vol 90:11924-11928 12/93).

a. The claims 1-10 have been described above.

b. Tamura et al disclose the IL-6 receptor antibody designated MR16-1 (Abstract, page 11925, cols 1-2, bridging paragraph). Thus, the prior art references fully disclose to the public the subject matter of the claimed invention.

15. Claims 1-11 are rejected under 35 U.S.C. 102(a) as being anticipated by Taetle et al (J Natl Cancer Inst Vol 86(6):450 3/94).

a. The claims 1-11 have been described above.

b. Taetle et al teach the compositions containing monoclonal antibodies PM1, AUK 146-15, AUK 64-7 and AUK12-20 which specifically bind to the human IL-6R-alpha protein (see

page 450, cols 1-2, bridging paragraph and page 451, cols 1-2, bridging paragraph). Thus, the prior art references fully disclose to the public the subject matter of the claimed invention.

Claim Rejections - 35 U.S.C. § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1-10 and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (cited above), taken in view of Riechmann et al (Nature Vol 332 323-327, March 1988).

a. The claims 1-10 have been described above. Claim 12 is being interpreted as an antibody which comprises portions from two different sources, such as human and rodent portions. Claim 13 recites a reshaped human antibody and is being interpreted as a humanized antibody for the purposes of the obviousness rejections. Tamura et al has been discussed above with regards to pharmaceutical compositions comprising IL-6R antibodies. However, Tamura et al fails to provide the methods to make chimeric or reshaped humanized antibodies.

b. Riechmann et al teach the "reshaping of human antibodies for therapy" (see Title) in which a "human IgG1 antibody has been reshaped for serotherapy in humans by introducing the six hyper variable regions from the heavy- and light-chain domains of a rat antibody directed against human lymphocytes" (see Abstract). Riechmann et al fully disclose how one skilled in the art would use recombinant DNA techniques to sequence, clone, humanize and reshape a monoclonal antibody, with a reasonable expectation of success. Further, Riechmann et al provide one skilled in the art with the motivation to humanize the antibodies for use as human pharmaceutical. Riechmann et al teach that "the foreign immunoglobulin, however, can elicit an anti-globulin response which may interfere with therapy or cause complex hypersensitivity." (page

323, column 1, first full paragraph). Humanized "chimaeric antibodies have at least two advantages over mouse antibodies. First the effector functions can be selected or tailored as desired...Second, the use of human rather than mouse isotypes should minimize the anti-globulin responses during therapy by avoiding anti-isotypic antibodies" (see page 323, bridging paragraph, columns 1-2).

c. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have humanized and reshaped the IL-6R monoclonal antibody MR16-1 of Tamura et al by using the recombinant DNA techniques provided by Riechmann et al. Further, one of ordinary skill in the art would have been motivated to humanize an reshape the MR16-1 monoclonal antibody with a reasonable expectation of success since Riechmann et al have disclosed the benefits of having an antibody that contains the human constant regions and contains human framework residues in order to preserve antigen affinity. In addition, one of ordinary skill in the art would have had a reasonable expectation of success to humanize and reshape the murine MR16-1 antibody because Riechmann et al have demonstrated the successful humanization and reshaping of other mouse antibodies. For the obviousness rejections, the Examiner is interpreting a humanized, reshaped antibody as a chimeric antibody because it contains sequences from two different species. Therefore, as the disclosure has not provided any unexpected results arising from the humanization and reshaping of their monoclonal antibody, in absence of evidence to the contrary and in light of the reasoning set forth above, Claims 1-10 and 12-13 are unpatentable over the obvious combination of prior art.

20. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taetle et al (cited above), taken in view of Riechmann et al (cited above).

a. Claims 1-14 have been described above. Taetle et al has been discussed above with regards to compositions comprising IL-6R antibodies. However, Taetle et al fails to provide the methods to make chimeric or reshaped human antibody.

b. Riechmann has been discussed above with regards to teaching methods and motivation for making reshaped humanized and chimeric antibodies.

c. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have humanized the PM-1 monoclonal antibody of Taetle et al by using the recombinant DNA techniques provided by Riechmann et al. Further, one of ordinary skill in the art would have been motivated to humanize and reshape the PM-1 monoclonal antibody with a reasonable expectation of success since Riechmann et al have disclosed the benefits of having an antibody that contains the human constant regions and human framework residues in order to avoid anti-human antibody response and to maintain antigen affinity. In addition, one of ordinary skill in the art would have had a reasonable expectation of success in reshaping and humanizing the murine PM-1 antibody because Riechmann et al have demonstrated the successful reshaping and humanization of other mouse antibodies. Therefore, as the disclosure has not provided any unexpected results arising from the humanization and reshaping of the PM-1 monoclonal antibody, in absence of evidence to the contrary and in light of

the reasoning set forth above, Claims 1-14 are unpatentable over the obvious combination of prior art.

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Reeves, Ph.D., whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

23. Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**lila.feisee@uspto.gov**].

24. All Internet e-mail communications will be made of record in the application file. **PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122.** This is more

clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

25. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Julie C Reeves

Julie E. Reeves, Ph.D.

Patent Examiner

(703) 308-7553